Towards an intrinsic nucleofugality scale: The leaving group (LG) ability in CH_3LG model system

P. Jaramillo [a], L.R. Domingo [b], P. Pérez [c,d,*]

[a] *Departamento de Ciencias Químicas, Facultad de Ecología y Recursos Naturales, Universidad Andrés Bello, Republica 275, Santiago, Chile*
[b] *Instituto de Ciencia Molecular, Unidad de Química Orgánica Teórica, Universidad de Valencia, Polígono 'La Coma', 46980 Paterna, Valencia, Spain*
[c] *Departamento de Química, Facultad de Ciencias, Universidad de Chile, Casilla 653, Santiago, Chile*
[d] *Departamento de Física, Facultad de Ciencias, Universidad de Chile, Casilla 653, Santiago, Chile*

Abstract

For an important class of organic reactions in which a fragment of the reactants, the leaving group (LG) or nucleofuge (Z), is detached of the substrate bearing the bonding electron pair, the global electrophilicity index of the CH_3LG system is proposed as a reliable descriptor of the intrinsic nucleofugality of the LG. The model is illustrated by ranking within a unique relative scale, the LG ability of 28 functional groups commonly involved in substitution and elimination reactions in organic chemistry.

---

1. Introduction

Nucleofugality [1] is defined as the propensity of an atom or group of them to depart bearing the bonding electron pair in a heterolytic cleavage process. Such groups that denominate nucleofuges (Z) or leaving groups (LG) are mainly present in two kinds of processes, namely nucleophilic substitution and elimination reactions (see Scheme 1). Nucleophilic substitution and elimination reactions share the same kind of reagents, namely, a nucleophile or a base, and a substrate having a good LG [2–7].

In order to establish a nucleofugality scale the following points were established by Stirling [1]. The rate of a reaction will reflect the nucleofugality only if the LG departure is involved in the rate-determining step. Hence, it is necessary to know in detail the mechanism associated with it. Additionally, the differential interactions between the nucleophile and the nucleofuge in S_N2 reactions are difficult to quantify, like also the LG abilities in concerted processes. Therefore, a system with a wide range of LGs, whose mechanism is unequivocally known, is required to provide entire information about the nucleofugality concept.

The LG departure is a complex process involving several aspects that include for instance, the polarizability of the LG, the involved reaction mechanism, the basicity of the nucleophile, solvent effects, nucleophile–nucleofuge interactions, etc. [8–11]. Despite the complexity of the description of nuleofugality, the quantification of this concept by means of a reactivity index becomes an important subject to understand the reactivity and mechanisms of a wide variety of reactions in organic chemistry.

Experimentally, nucleofugality has been discussed in connection with the pK_a's in water of the conjugated acid of the LG. Boyd [12] found a correlation between pK_a values of the acid (LG-H), the C-LG bond strength, and the

$$\mathrm{Nu\!:} + \mathrm{R\text{-}Z} \rightarrow \mathrm{Nu\text{-}R} + \mathrm{:Z}$$

(a) Nucleophilic substitution reaction

$$\mathrm{B\!:} + \mathrm{XCH_2\text{-}CH_2Z} \rightarrow \mathrm{BH} + \mathrm{XCH{=}CH_2} + \mathrm{:Z}$$

(b) 1,2-Elimination reaction

Scheme 1.

---

[*] Corresponding author. Fax: +56 2 2712973.
E-mail address: pperez@macul.ciencias.uchile.cl (P. Pérez).

rate of reaction of the free LG with methyl iodide. The author found that for a series of 11 LGs, the nucleofugality did not vary monotonically with the acidity of LG-H. The observed trend was apparent and in the expected direction [12]. Boyd [12] also stressed that properties like electron affinity, polarizability and inductive effects are expected to be related to the LG ability. On the other hand, Stirling et al. [13] suggested that reactivity shows no correlation with the molecular properties discussed by Boyd [12] for neutral groups, and that even in 1,2-eliminations, good correlations exist if the variation in the LG is small. Bartoli and Todesco [14] proposed an empirical linear relationship to describe the effect of the nucleofuge by considering the basicity difference and polarizability of the nucleophiles, the substrate and the LGs in aromatic nucleophilic substitution. The empirical relation found was in agreement with the experimental data reported by Bunnett [15–17], in the sense that the rate of replacement of polarizable nucleofuges increased with the increasing polarizability of the LG. Rappoport et al. [18–20] have studied the stereochemistry of vinylic substitution reactions and the influence of the nucleofuge in the rate-determining step of the process. These authors suggested that the rate-determining step of vinylic substitution reactions should correspond to the formation of a carbanion intermediate, with the subsequent nucleofuge departure [18–20]. The majority of these works stress that a basic requisite to describe nucleofugality is the knowledge of the reaction mechanism.

It is worth emphasizing at this point, that global electrophilicity index [21], ω, defined within the DFT context, encompasses all the three ingredients mentioned by Boyd [12] within a single number: the electron affinity appears averaged with the ionization potential in a parent concept, namely the electronic chemical potential which is related to electronegativity [22] and chemical softness which is intimately related to polarizability [23]. Inductive effects on the other hand, have been shown to be well described by local electrophilicity, in the form of local responses at the active site induced by chemical substitution [24–27]. In consequence, the global electrophilicity index [21] can be an useful descriptor to rank the intrinsic nucleofugality of the LG. We have recently stressed that the electrophilicity index is a good descriptor to describe the intrinsic electronic contribution to the Hammett substituent constant [26]. Our results showed that the calculated electrophilicity index, ω, for a series of substituted ethylenes may be used to make reliable estimates of the intrinsic electronic contributions, $\sigma_e(\omega)$, to the σ_p constants of Hammett for a series including 42 functional groups commonly present in organic compounds [26].

The nucleofugality concept has received less attention from a theoretical point of view. Recently, Ayers et al. [28,29] have proposed a model to study the quality of the LGs in substitution and elimination reactions. The proposed model by Ayers et al. [28] claim the idea that a nucleofuge must take an entire electron with it upon dissociation suggesting that the destabilization that occurrs by forcing a molecule to accept an entire electron will be related to the nucleofugality [28]. The authors emphasized that their model measures the inherent quality of a LG, without considering other external effects (molecule interactions, solvent effects), stressing that the molecule propensity gains electron from the substrate under dissociation [28,29]. Therefore, the authors have related the LG property with the ionization potential and electron affinity using a quadratic model for the dependence of the energy with the number of the electrons [28,29]. In general, the model reproduces fairly well the nucleofugality of a reduced number of known LGs [28,29].

In this Letter, an intrinsic LG index is proposed to quantitatively rank, within a unique scale of reactivity, the LG ability of a series of atoms or groups of them currently present as nucleofuges in organic chemistry. The proposed model will measure the propensity of a molecular fragment, the LG, to get an additional electronic charge from a molecule and dissociate as leaving group in its initial stage. We have used a reduced model consisting a series of known LG attached to the methyl group to form the CH_3LG model system. Since along the heterolytic substrate-LG breaking bond the LG detaches from the substrate bearing the bonding pair, it is expected that the ability of the LG will be related to the electrophilicity of the LG. Because the CH_3-fragment is hard, we expect the main part of the regional responses to be reasonably well described by electrophilic activation on the electron-withdrawing (EW) substituted methyl derivative, by analyzing the intrinsic global electrophilicity of a wide range of CH_3LG model systems.

2. Model equations

The global electrophilicity index ω, which measures the stabilization in energy when the system acquires an additional electronic charge ΔN from the environment, has given the following expression [21]:

$$\omega = \frac{\mu^2}{2\eta}, \qquad (1)$$

in terms of the electronic chemical potential μ and the chemical hardness η [22]. These quantities may be approached in terms of the one electron energies of the frontier molecular orbital HOMO and LUMO, ε_H and ε_L, as $\mu \approx \frac{\varepsilon_H + \varepsilon_L}{2}$ and $\eta \approx \varepsilon_L - \varepsilon_H$, respectively [21,22,30]. The electrophilicity index encompasses both, the propensity of the electrophile to acquire an additional electronic charge driven by μ^2 (the square of electronegativity, $\chi = -\mu$), and the resistance of the system to exchange electronic charge with the environment described by η. A good electrophile is, in this sense, characterized by a high value of μ and a low value of η.

3. Computational details

The global electrophilicity values for a series of CH_3LG model systems needed to classify the LG ability were evaluated using Eq. (1). The electronic chemical potential, μ, and chemical hardness, η, were evaluated in terms of the one electron energies of the FMOs, HOMO and LUMO, as shown in Section 2. The calculations were performed at the ground state (GS) of the molecules using the B3LYP/6-31G* level of theory, implemented in the Gaussian 98 package of programs [31]. Additional calculations were performed at the GS of the molecules using the B3LYP/LANDL2DZ level of theory using pseudopotentials for heavy atoms, also implemented in the Gaussian 98 package of programs [31]. These systems are marked with an asterisk in Table 1.

4. Results and discussion

The global electrophilicity values for a series of 28 CH_3LG model systems are shown in Table 1. The last column displays the global ω values in decreasing order for the corresponding methyl derivatives. This order, in our model represents the ability of the LGs or nucleofugality, and it is in agreement with the approximate order of departure ability from the substrate of some LGs presented in Table 10.10 of March's Advanced Organic Chemistry [32]. It is worth to mention that the order of LG ability is about the same for S_N1 and S_N2 reactions [32]. The ability of the LG measured by ω index moves from 9.73 eV for $–N_2^+$ to 0.23 eV for $–NH_2$. There are around 9 units of eV between the ends of this series of CH_3LG model systems. N_2^+ is predicted to be the best LG whereas NH_2 is the poorest in the series [32]. We will do comparisons between subseries. For instance, the order of the nucleofugality shown in Table 1 for the sulfonic acid derivatives: CH_3-$OSO_2CF_3 > CH_3$-$OSO_2PhCH_3 > CH_3$-OSO_2CH_3 is in reasonable agreement with the experimental outcome. The feasibility of LG is related with the increase of the EW behavior of the substituent on the sulfonic acid; $–CF_3 > –PhCH_3 > –CH_3$. Note that this subseries constitutes the best LGs of the neutral molecules given in Table 1, having a larger nucleofugality than –I fragment in agreement with results from Table 10.10 of [32].

Table 1
Potential (μ), chemical hardness (η), global and global electrophilicity (ω)[a]

Model system	LG	μ (a.u.)	η (a.u.)	ω (eV)
$CH_3–N_2^+$	N_2^+	–0.507	0.359	9.73
$CH_3–H_2O^+$	H_2O^+	–0.431	0.391	6.47
$CH_3–OHCH_3^+$	CH_3OH^+	–0.392	0.373	5.62
$CH_3–NH_3^+$	NH_3^+	–0.408	0.442	5.14
$CH_3–O(CH_3)_2^+$	$O(CH_3)_2^+$	–0.356	0.357	4.84
$CH_3–S(CH_3)_2^+$	$S(CH_3)_2^+$	–0.346	0.339	4.81
$CH_3–N(Me)_3^+$	$N(Me)_3^+$	–0.356	0.448	3.85
$CH_3–SO_2F$	SO_2F	–0.161	0.339	1.03
$CH_3–ONO_2$	ONO_2	–0.191	0.251	1.98
$CH_3–OSO_2CF_3$	$CF_3SO_3^*$	–0.190	0.258	1.91
$CH_3–OSO_2ArCH_3$	$OSO_2ArCH_3^*$	–0.163	0.221	1.63
$CH_3–CO_2CF_3$	$CF_3CO_2^*$	–0.168	0.274	1.40
$CH_3–I$	I*	–0.148	0.222	1.34
$CH_3–OSO_2CH_3$	$OSO_2CH_3^*$	–0.160	0.262	1.33
$CH_3–SCN$	SCN	–0.148	0.238	1.25
$CH_3–NCS$	NCS	–0.127	0.235	0.94
$CH_3–OCOH$	OCOH	–0.139	0.289	0.91
$CH_3–Br$	Br	–0.135	0.275	0.90
$CH_3–CN$	CN	–0.145	0.363	0.79
$CH_3–OCOCH_3$	$OCOCH_3$	–0.127	0.284	0.78
$CH_3–Cl$	Cl	–0.135	0.322	0.77
$CH_3–SH$	SH	–0.104	0.264	0.56
$CH_3–H$	H	–0.136	0.507	0.49
$CH_3–F$	F	–0.113	0.438	0.40
$CH_3–SCH_3$	SCH_3	–0.087	0.261	0.39
$CH_3–OH$	OH	–0.095	0.340	0.36
$CH_3–OCH_3$	OCH_3	–0.080	0.344	0.25
$CH_3–NH_2$	NH_2	–0.072	0.313	0.23

[a] HOMO and LUMO values in a.u.; electronic chemical potential (μ) chemical hardness (η) in a.u.; global electrophilicity values (ω) in eV. Calculations were performed at B3LYP/6-31G(d) level of theory in all the systems, with the only exception of those systems marked with asterisk, that were calculated using the pseudopotential LANL2DZ for S, F and I atoms.

On the other hand, within the halogen family, the nucleofugality order is: I > Br > Cl > F. In this case, the nucleofugality order reproduces the strength of the halic acids (HI(–10) > HBr(–9) > HCl(–7) > HF(3.2), pK_a values in parenthesis). Thus, within a family of compounds the nucleofugality and the pK_a are well correlated, which is in agreement with the knowledge concerning about the quality of the LGs [32]. It is interesting to mention here, that our model of electrophilicity provides a measure for the stability of anions: $I^- > Br^- > Cl^- > F^-$ (i.e., upon dissociation), although for a limited family of systems. Note that the ω index [21] was defined as energy stabilization when the system acquires an additional electronic charge from the environment, hence from this point of view this result is interesting. Notice that the ω value for CH_3-I ($\omega = 1.34$ eV) was obtained using the LANL2DZ pseudopotential only for I atom. C and H atoms were calculated using the standard basis set presented in Section 3.

The acyl derivatives of the alcohols, –OCOR, present also a good correlation with the pK_a of the corresponding carboxylic acids. For instance, the nucleofugality order $–OCOCF_3 > –OCOH > –OCOCH_3$ is consistent with the strength of the carboxylic acids $F_3CCO_2H(0.5) > HCO_2H$ $(3.75) > CH_3CO_2H(4.76)$, (pK_a values in parenthesis). In a similar behavior to the halic acid series, the trend of the LG ability in the acyl derivatives is in the direction of the decrease of the pK_a values [12].

At the bottom of Table 1, it is found –H, –OH, $–OCH_3$ and $–NH_2$ groups classified as poor LGs in nucleophilic substitution reactions (see Table 10.10 of [32]). However in a strong acid medium protonation of the poor leaving groups, –OH, $–OCH_3$, $–NH_2$ groups, are converted in the very good leaving groups $–OH_2^+$, $–OHCH_3^+$ and $–NH_3^+$ ones. In Table 1, these species and other positively charged, like $–O(CH_3)_2^+$, $–S(CH_3)_2^+$ and $–N(Me)_3^+$ present the highest values for ω index and they may be classified as very good LGs. Note that in Table 1, $CH_3 – OH_2^+$ is positioned above CH_3-I and CH_3-Br, while experimentally it is below them. The larger solvation of ROH_2^+ than the neutral R-I and R-Br species, together with the low concentration of the former in the reaction media can be responsible for this shift.

Finally, it may be seen a fairly good correlation between log(k_{rel}) and the electrophilicity index for the halogen leaving groups (see Fig. 1). The experimental values correspond to a concerted alkene-forming elimination reaction: $\mathrm{EtO^-} + \mathrm{PhCH_2CH_2\text{-}LG}$ (LG = F, C, Br, I) → $\mathrm{EtOH} + \mathrm{PhCH{=}CH_2} + \mathrm{LG}$ [8]. The value of the regression coefficient, $R = 0.95$, is quite reasonable considering the order of magnitude of the rate constants. On the other hand, a comparison between log(k_{rel}) and the pK_a values for the halic acid series is shown in Fig. 2. It may seen that the regression coefficient ($R = 0.93$) between both variables is not as good as the comparison shown in Fig. 1. It is worth to mention that the electrophilicity concept is a kinetic one [33]. For this reason, the comparison between log(k_{rel}) and the ω index, as nucleofugality index model, shown in Fig. 1 is more appropriate than the comparison between log(k_{rel}) and pK_a values, since the pK_a concept is a thermodynamic one. Although the comparison is limited to the subseries of halogen LGs (Fig. 1), it can be an useful proof to test the proposed model to measure the LG ability in a specific reaction.

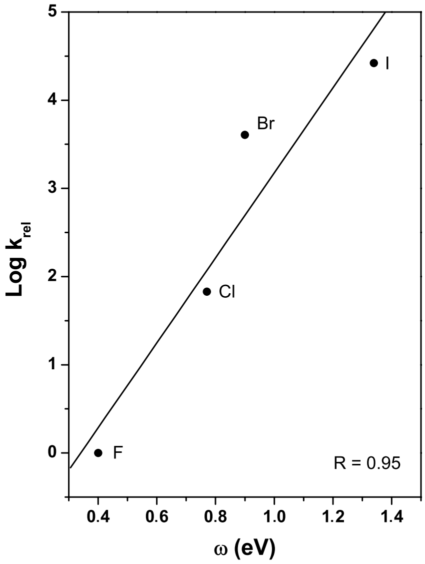

Fig. 1. Comparison between log(k_{rel}) and the electrophilicity index, ω, for the halogen leaving groups for the elimination reaction $\mathrm{EtO^-} + \mathrm{PhCH_2CH_2Z}$ (Z = F, C, Br, I) → $\mathrm{EtOH} + \mathrm{PhCH{=}CH_2} + \mathrm{Z}$.

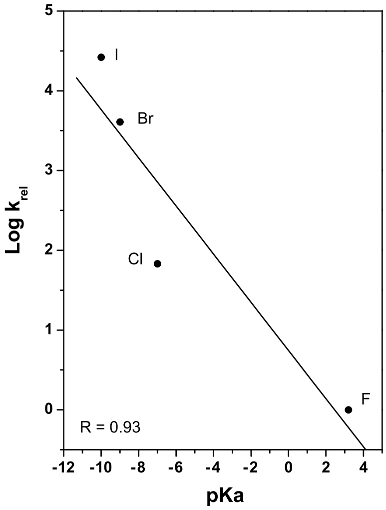

Fig. 2. Comparison between log(k_{rel}) and the pK_a values for the halic acids series. See the text for details.

In summary, it may be seen that from the present model it is not possible to get a unique nucleofugality scale for the whole system, due to the complexity for considering all the factors involved in the nucleofugality concept. The discussion of the ability of the LG has been done only for families or series of systems, whose general ability is known. The Stirling's statements to establish a nucleofugality hierarchy should be considered to construct both, experimental and theoretical nucleofugality scales.

Studies on specific reactions, mechanisms and solvent effects associated to them to find correlations, if existing, between the proposed nucleofugality index and theoretical and kinetic parameters are in progress in our group.

5. Concluding remarks

In this Letter, we propose that the electrophilicity index ω of the $\mathrm{CH_3LG}$ model system assesses the nucleofugality or the ability of the leaving groups when it is detached of the substrate with the bonding electronic pair for different numbers of the systems. The present model allows us to measure the intrinsic ability of a LG in absence of the solvent effects and other specific interactions. These effects are not negligible in experimental systems. However, we stress that the proposed model can be an useful guide to the quality of the LGs, measuring the propensity of a molecular fragment to receive an additional electronic charge from the substrate and dissociate as leaving group. Certainly, external effects may modify the ability of the leaving groups depending on the specific reaction conditions. Indeed, the model can be improved including solvent effects to specific reactions under study.

The model is illustrated by ranking within a unique relative scale, the LG ability of 28 functional groups commonly involved in substitution and elimination reactions in organic chemistry. Our theoretical scale is in clear agreement with that for the LG ability proposed from the experimental data of March's book. However, in order to satisfy the important requisites claimed by Stirling to get a nucleofugality scale it is necessary to have systems with a wide range of LG, whose mechanism is unequivocally known to provide entire information about the nucleofugality concept.

Acknowledgments

This work was supported by Fondecyt, Grants 1020069, DI-17-04 from the Universidad Andrés Bello, and Millennium Nucleus for Applied Quantum Mechanics and Computational Chemistry, Grant No. P02-004-F (Mideplan and Conicyt). L.R.D thanks Fondecyt, Grant 7020069, for the financial support and Universidad Andrés Bello for the warm hospitality. P.J. is grateful to the Universidad Andrés Bello for a graduate fellowship.

References

[1] C.J.M. Stirling, Acc. Chem. Res. 12 (1979) 198.

[2] F.A. Carey, R.J. Sundberg, Advanced Organic Chemistry, Part A: Structure and Mechanism, Plenum, New York, 1984.

[3] R.J. Sundberg, F.A. Carey, Advanced Organic Chemistry, Part B: Reactions and Synthesis, Plenum, US, 2001.

[4] C.K. Ingold, Structure and Mechanism in Organic Chemistry, Cornell University Press, Ithaca, New York, 1969.

[5] T.H. Lowry, K.S. Richardson, Mechanism and Theory in Organic Chemistry, third edn., Harper Collins Publishers, New York, 1987.

[6] A. Streitwieser Jr., Solvolytic Displacement Reactions, McGraw-Hill, New York, 1962.

[7] S. Gronert, Chem. Rev. 101 (2001) 329.

[8] F. Cockerill, R.G. Harrison, in: S. Patai (Ed.), The Chemistry of Double-bonded Functional Groups, Wiley, New York, 1977.

[9] S. Gronert, A.F. Fagin, K. Okamoto, S. Mogali, L.M. Pratt, J. Chem. Am. Soc. 126 (2004) 126.

[10] M.E. Jones, G.B. Ellison, J. Chem. Am. Soc. 111 (1989) 1645.

[11] S. Gronert, Acc. Chem. Res. 36 (2003) 848.

[12] D.B. Boyd, J. Org. Chem. 50 (1985) 885.

[13] D.R. Marshall, P.J. Thomas, C.J.M. Stirling, J. Chem. Soc. Chem. Commun. (1975) 940.

[14] G. Bartoli, P.E. Todesco, Acc. Chem. Res. 10 (1977) 125.

[15] J.F. Bunnett, J. Am. Chem. Soc. 79 (1957) 5969.

[16] J.F. Bunnett, E.W. Garbisch Jr., K.M. Pruitt, J. Am. Chem. Soc. 79 (1957) 385.

[17] J.F. Bunnett, R.H. Garst, J. Am. Chem. Soc. 87 (1965) 3875.

[18] B. Avramovitch, Z. Rappoport, J. Am. Chem. Soc. 110 (1988) 911.

[19] B. Avramovitch, P. Weyerstahl, Z. Rappoport, J. Am. Chem. Soc. 109 (1987) 6687.

[20] Z. Rappoport, A. Topol, J. Org. Chem. 54 (1989) 5967.

[21] R.G. Parr, L.v. Szentpály, S. Liu, J. Am. Chem. Soc. 121 (1999) 1922.

[22] R.G. Parr, W. Yang, Density Functional Theory of Atoms and Molecules, Oxford University Press, New York, 1989.

[23] Y. Simón-Manso, P. Fuentealba, J. Phys. Chem. A 102 (1998) 2029.

[24] L.R. Domingo, M.J. Aurell, P. Pérez, R. Contreras, Tetrahedron 58 (2002) 4417.

[25] L.R. Domingo, M.J. Aurell, P. Pérez, R. Contreras, J. Phys. Chem. A 106 (2002) 6871.

[26] L.R. Domingo, P. Pérez, R. Contreras, J. Org. Chem. 68 (2003) 6060.

[27] A. Aizman, R. Contreras, P. Pérez, Tetrahedron 61 (2005) 889.

[28] P.W. Ayers, J.S.M. Anderson, L.J. Bartolotti, Int. J. Quant. Chem. 101 (2005) 520.

[29] P.W. Ayers, J.S.M. Anderson, J.I. Rodriguez, Z. Jawed, Phys. Chem. Chem. Phys. 7 (2005) 1918.

[30] R.G. Parr, R.G. Pearson, J. Am. Chem. Soc. 105 (1983) 7512.

[31] M.J. Frisch et al., GAUSSIAN 98 Revision A.6, Gaussian Inc., Pittsburgh, PA, 1998.

[32] M.B. Smith, J. March, March's Advanced Organic Chemistry, John Wiley & Sons Inc., New York, 2001.

[33] H. Mayr, M. Patz, Angew. Chem., Int. Ed. Engl. 33 (1994) 938.